



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2018-N-3065]

Memorandum of Understanding Addressing Certain Distributions of Compounded Drug

Products Between the States and the Food and Drug Administration; Revised Draft; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability; withdrawal.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is announcing the availability for public comment of a revised draft standard memorandum of understanding (MOU) entitled “Memorandum of Understanding Addressing Certain Distributions of Compounded Drug Products Between the State of [insert State] and the U.S. Food and Drug Administration” (revised draft standard MOU). The revised draft standard MOU describes the responsibilities of a State that chooses to sign the MOU in investigating and responding to complaints related to compounded drug products compounded in the State and distributed outside the State and in addressing the interstate distribution of inordinate amounts of compounded drug products.

FDA is also announcing the withdrawal of an earlier draft standard MOU entitled “Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drug Products Between the State of [insert State] and the U.S. Food and Drug Administration,” which was issued in February 2015 (2015 draft standard MOU). The 2015 draft standard MOU is superseded by the revised draft standard MOU.

DATES: FDA is withdrawing its draft standard MOU that published on February 19, 2015 (80 FR 8874), as of [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Submit either electronic or written comments on the revised draft standard MOU by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*], to ensure that the Agency considers your comment on this draft MOU before it begins work on the final version of the MOU. Submit either electronic or written comments on information collection issues under the Paperwork Reduction Act of 1995 by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] (see the “Paperwork Reduction Act of 1995” section of this document).

ADDRESSES: You may submit comments on the MOU at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else’s Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see “Written/Paper Submissions” and “Instructions”).

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in “Instructions.”

Instructions: All submissions received must include the Docket No. FDA-2018-N-3065 for “Memorandum of Understanding Addressing Certain Distributions of Compounded Drug Products Between the States and the Food and Drug Administration; Revised Draft; Availability.” Received comments will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its

consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Submit written requests for single copies of the draft MOU to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft document.

FOR FURTHER INFORMATION CONTACT: Sara Rothman, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 5197, Silver Spring, MD 20993-0002, 301-796-3110.

SUPPLEMENTARY INFORMATION:

I. Background

Section 503A of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 353a) describes the conditions that must be satisfied for drug products compounded by a licensed pharmacist or licensed physician to be exempt from the following sections of the FD&C Act: (1) section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)) (concerning current good manufacturing practice (CGMP) requirements), (2) section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use), and (3) section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications or abbreviated new drug applications).

One of the conditions to qualify for the exemptions listed in section 503A of the FD&C Act is that: (1) the drug product is compounded in a State that has entered into an MOU with FDA that addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to drug products distributed outside such State or (2) if the drug product is compounded in a State that has not entered into such an MOU, the licensed pharmacist, pharmacy, or physician does not distribute, or cause to be distributed, compounded drug products out of the State in which they are compounded in quantities that exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician (5 percent limit) (see section 503A(b)(3)(B)(i) and (ii) of the FD&C Act).

Section 503A(b)(3)(B) of the FD&C Act directs FDA to develop, in consultation with the National Association of Boards of Pharmacy (NABP), a standard MOU for use by the States in complying with section 503A(b)(3)(B)(i).

II. Previous Efforts to Develop a Standard MOU

In the *Federal Register* of January 21, 1999 (64 FR 3301), FDA announced the availability for public comment of a draft standard MOU, developed in consultation with NABP (1999 draft standard MOU). Over 6,000 commenters submitted comments on the 1999 draft standard MOU. Because of litigation over the constitutionality of the advertising, promotion, and solicitation provision in section 503A of the FD&C Act,¹ the draft standard MOU was not completed. In 2013, section 503A of the FD&C Act was amended by the Drug Quality and Security Act (DQSA) (Pub. L. 113-54) to remove the advertising, promotion, and solicitation provisions that were held unconstitutional, and FDA took steps to implement section 503A, including the provisions on the MOU. In the *Federal Register* of February 19, 2015 (80 FR 8874), FDA withdrew the 1999 draft standard MOU and issued the 2015 draft standard MOU for public comment. FDA received more than 3,000 comments on the 2015 draft standard MOU. By this notice, FDA is withdrawing the 2015 draft standard MOU, and the revised draft standard MOU made available today supersedes the 2015 draft standard MOU.

III. 503A Guidance

Immediately after the enactment of the DQSA, in December 2013, the Agency published a draft guidance on section 503A of the FD&C Act entitled “Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act” (2013 draft

¹ The conditions of section 503A of the FD&C Act originally included restrictions on the advertising or promotion of the compounding of any particular drug, class of drug, or type of drug and the solicitation of prescriptions for compounded drugs. These provisions were challenged in court and held unconstitutional by the U.S. Supreme Court in 2002. See *Thompson v. Western States Med. Ctr.*, 535 U.S. 357 (2002).

503A guidance) (see 78 FR 72901, December 4, 2013) announcing the availability of the draft guidance). The 2013 draft 503A guidance described FDA's proposed policy with regard to specific provisions of section 503A of the FD&C Act that require rulemaking or other action by FDA, such as the MOU provisions. Several commenters on the 2013 draft 503A guidance offered FDA their views on the MOU provisions of section 503A of the FD&C Act. FDA considered these comments in developing the 2015 draft standard MOU and the revised draft standard MOU it is issuing today. The final 503A guidance (available at <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm469119.pdf>), published July 2, 2014 (see 79 FR 37742 announcing the availability of the final 503A guidance), states that FDA does not intend to enforce the 5 percent limit on distribution of compounded drug products out of the State in which they are compounded until after FDA has finalized an MOU and made it available to the States for their consideration and signature. After considering any comments on the revised draft standard MOU submitted to this docket, FDA intends to finalize the MOU and make it available for signature by individual States. FDA will determine at the time of publication of the final MOU how long it will allow States to consider whether to sign the MOU before FDA begins to enforce the 5 percent limit in those States that have not signed an MOU. As discussed below, FDA is proposing a 180-day period.

IV. Revised Draft Standard MOU

FDA has now developed a revised draft standard MOU on which it is soliciting public comment. FDA has consulted with NABP in developing this revised draft standard MOU. FDA also considered the comments submitted on the 2015 draft standard MOU, as well as comments on the MOU provisions it received in connection with the 2013 draft 503A guidance. Below,

FDA has summarized and discussed key provisions of the revised draft standard MOU and, where appropriate, summarized changes that the Agency made in the revised draft standard MOU. Drug products intended for veterinary use, repackaged drug products, biological products subject to licensure through a biologics license application under section 351 of the Public Health Service Act (42 U.S.C. 262), and drug products compounded by outsourcing facilities are not the subject of the revised draft standard MOU.

A. Investigation of Complaints

The revised draft standard MOU provides that States that enter into the MOU will agree to:

- Investigate complaints relating to drug products compounded by a pharmacist in the State and distributed outside the State by a pharmacy, including complaints about adverse drug experiences or product quality issues to, among other things, take steps to assess whether there is a public health risk and whether such risk is adequately contained;
- Take action, in accordance with and as permitted by State law, to ensure that the relevant compounding pharmacy investigates the root cause of the problem and addresses any public health risk identified in relation to the complaint;
- Notify FDA as soon as possible, but no later than 3 business days, after receiving any complaints relating to a drug product compounded by a pharmacist in the State and distributed outside the State involving a serious adverse drug experience or serious product quality issue, and provide FDA with certain information about the complaint, including the following:
 - Name and contact information of the complainant;
 - Name and address of the pharmacy/physician that is the subject of the complaint;

- Description of the complaint, including a description of any compounded drug product that is the subject of the complaint; and
- State's initial assessment of the validity of the complaint relating to a compounded drug product distributed outside the State, if available;
- Subsequent to this notification, provide FDA with the results (description and date of any State actions) of its investigation;
- Notify the appropriate regulator of physician compounding within the State of any complaints about adverse drug experiences or product quality issues related to drug products compounded by a physician in the State and distributed outside the State; and
- Maintain records of the complaints it receives, the investigation of each complaint, and any response to or action taken as a result of a complaint, beginning when the State receives notice of the complaint. The revised draft standard MOU says that the State agrees to maintain these records for at least 3 years, beginning on the date of final action or the date of a decision that the complaint requires no action.

The types of complaints of compounded drug products that should be investigated include *any* adverse drug experience and product quality issues. Even non-serious adverse drug experiences and product quality issues can be indicative of problems at a compounding facility that could result in product quality defects leading to serious adverse drug experiences if not corrected. For example, inflammation around the site of an injection can indicate drug product contamination from inadequate sterile practices at the compounding pharmacy. If the pharmacy has inadequate sterile practices, other more serious contamination could result in serious adverse events.

The revised draft standard MOU does not include specific directions to the States relating to how to conduct their investigation of complaints. Rather, as recommended by comments submitted to FDA previously, the details of such investigations are left to the States' discretion. For example, a State may review an incoming complaint describing an adverse drug experience and determine that such a complaint does not warrant further investigation. In other cases, a State may determine that an incoming complaint contains insufficient information and investigate further to determine appropriate action.

States signing the revised draft standard MOU would agree to notify FDA about certain complaints and provide FDA with certain information about the complaints so FDA could investigate the complaints itself, or take other appropriate action.² FDA received comments that it was not feasible for States to notify FDA of certain complaints within a 72-hour timeframe, as described in the 2015 draft standard MOU. Comments noted that gathering the information requested for submissions within just 72 hours might be difficult for States, particularly given that this period might overlap with a weekend or holiday. Some comments requested up to 7 days to provide the notification, but several others suggested that FDA revise the notification period to 3 *business* days. FDA has now revised the MOU to reflect the latter approach. The revised draft standard MOU provides that notification will occur as soon as possible, but no later than 3 business days after the State receives the complaint. This period will continue to facilitate early Federal/State collaboration on serious adverse drug experiences and serious product quality issues that have the potential to affect patients in multiple States, while providing for notification in a time frame that is more feasible for the States. We note that FDA has staff on call 24 hours a day to receive information in emergency situations.

² FDA is currently considering whether to propose regulations or issue guidance documents to further its implementation of section 503A(b)(3)(B) of the FD&C Act. Notice of any such action will be provided in the *Federal Register*.

Comments also expressed concern that certain provisions regarding complaint investigation that States entering into the MOU would agree to may require States to take action not permitted by State law and may imply that, after taking action, the State has made a legal determination that the complaint has been resolved. The revised draft standard MOU clarifies that the State should investigate and take action that the State considers to be appropriate with respect to the complaint in accordance with and as permitted by State law. FDA has also clarified that, by signing the MOU, the State agrees to assess the existence of a public health risk associated with the complaint and whether such risk is adequately contained rather than make definitive determinations of risk or confirm containment.

B. Inordinate Amounts

The revised draft standard MOU provides that States that enter into the MOU will agree to:

- On an annual basis (at minimum), identify, using surveys, reviews of compounding records during inspections of compounding pharmacies, or other mechanisms available to the State, compounding pharmacies that distribute inordinate amounts of compounded drug products interstate by collecting information regarding the following:
 - Total number of prescription orders for compounded drug products distributed or dispensed intrastate, and
 - Total number of prescription orders for compounded drug products distributed interstate;
- If the State becomes aware of a physician who is distributing compounded drug products interstate, coordinate with the appropriate regulator of physician compounding within the State to determine, using surveys, reviews of records during inspections, or other

mechanisms available to the State, whether the physician distributes inordinate amounts of compounded drug products interstate by collecting information regarding the following:

- Total number of prescription orders for compounded drug products distributed or dispensed intrastate, and
- Total number of prescription orders for compounded drug products distributed interstate;
- For pharmacies or physicians that have been identified as distributing inordinate amounts of compounded drug products interstate, collect information regarding the following:
 - Total number of prescription orders for sterile compounded drugs distributed interstate;
 - Number of States in which the compounding pharmacy or physician is licensed or into which the compounding pharmacy or physician distributes compounded drug products; and
 - Whether the State inspected for and found during its most recent inspection that the compounding pharmacy or physician distributed compounded drug products without valid prescriptions for individually identified patients;
- Notify FDA if the State identifies any pharmacy or physician within its jurisdiction that has distributed inordinate amounts of compounded drug products interstate; and
- Provide FDA with the following information regarding pharmacies or physicians that distributed inordinate amounts of compounded drug products interstate:
 - Name and address of the pharmacy/physician;

- Total number of prescription orders for compounded drug products distributed or dispensed intrastate;
- Total number of prescription orders for compounded drug products distributed interstate;
- Total number of prescription orders for sterile compounded drugs distributed interstate,
- Number of States in which the compounding pharmacy or physician is licensed or into which it distributes compounded drug products, and
- Whether the State inspected for and found during its most recent inspection that the compounding pharmacy or physician distributed compounded drug products without valid prescriptions for individually identified patients.

In the revised draft standard MOU, a pharmacy or physician is considered to have distributed an inordinate amount of compounded drug products interstate if the number of prescription orders for compounded drug products distributed interstate during any calendar month is greater than 50 percent of the number of prescription orders for compounded drug products dispensed or distributed both intrastate and interstate by such pharmacy or physician during that calendar month. This concept would be called the 50 percent threshold.

Section 503A of the FD&C Act reflects Congress' recognition that compounding may be appropriate when it is based on receiving a valid prescription or notation from a prescribing practitioner for an identified individual patient. However, drug products compounded under section 503A are not required to demonstrate that they are safe or effective, bear adequate directions for use, or conform to CGMP. Congress, therefore, imposed strict limits on the

distribution of drug products compounded under section 503A to protect the public health and the integrity of the drug approval process.

In particular, Congress did not intend for compounders operating under these statutory provisions to grow into conventional manufacturing operations making unapproved drugs, operating a substantial proportion of their business interstate, without adequate oversight. Although other provisions of the FD&C Act apply to State-licensed pharmacies and physicians that may qualify for the exemptions under section 503A of the FD&C Act (e.g., the adulteration provisions for making drugs under insanitary conditions), and although FDA may take action in appropriate cases against compounders that violate these provisions or that operate outside of the conditions in section 503A, Congress recognized that these compounders are primarily overseen by the States. If a substantial proportion of a compounder's drugs are distributed outside a State's borders, adequate regulation of those drugs poses significant challenges to State regulators. States face logistical, regulatory, and financial challenges inspecting compounders located outside of their jurisdiction. In addition, if a compounder distributes drugs to multiple States, it can be very difficult to gather the scattered information about possible adverse events associated with those drugs, connect them to the compounder, and undertake coordinated action to address a potentially serious public health problem.

Therefore, as a baseline measure, section 503A(b)(3)(B) of the FD&C Act limits the distribution of compounded drug products outside of the State in which they are compounded to 5 percent of the total prescription orders dispensed or distributed by a licensed pharmacist, pharmacy or physician. It then directs FDA, in consultation with NABP, to develop a standard MOU that addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to

drug products compounded in and distributed outside such State. Implementation of this provision involves FDA describing what inordinate amounts means and providing a mechanism for addressing interstate distribution of inordinate amounts of compounded drug products, as long as the States agree to appropriately investigate complaints relating to drug products compounded in and distributed out of the State.

In the 2015 draft standard MOU, FDA proposed that distribution interstate up to a 30 percent limit would not be inordinate, and that States entering into the MOU would agree to take action regarding pharmacists, pharmacies, or physicians that distribute inordinate amounts of compounded drugs interstate. FDA received a number of comments indicating that certain pharmacies, such as pharmacies located near state borders and home infusion pharmacies, distribute more than 30 percent of their compounded drugs to patients interstate because, for example, the patients are located in another nearby State, or because few pharmacies compound a particular drug to treat an uncommon condition for patients dispersed throughout the country. The comments noted that the proposed definition of inordinate amounts and the proposed provision in which States agree to take action could prevent such pharmacies from fulfilling patients' medical needs for the drugs that they supply. Other comments expressed concern about instances in which pharmacies are located near a State border and distribute compounded drugs to the other side of that border. FDA also received general comments questioning the Agency's basis for the 30 percent limit and indicating that it was too low. Some comments suggested that FDA increase the limit, including a suggestion to increase it to 50 percent.

The revised draft standard MOU addresses these comments in two respects. First, it would remove the provision in the 2015 draft standard MOU that States agree to take action with respect to the distribution of inordinate amounts of compounded drug products interstate.

Second, it would change what is considered “inordinate amounts” from a 30 percent limit to a 50 percent threshold.

With respect to State action, the revised draft standard MOU instead provides that States entering into the MOU would agree to inform FDA of compounders that have distributed an inordinate amount of compounded drug products interstate. The Agency does not intend to take action against a compounder located in a State that has entered into the MOU solely because the compounder has exceeded the threshold for inordinate amounts. Rather, FDA proposes that States collect further information on compounders that have distributed inordinate amounts interstate and provide this information to FDA to help inform inspectional priorities.

States generally have day-to-day oversight responsibilities over State-licensed pharmacies, pharmacists, and physicians. In general, FDA considers a pharmacy or physician that distributes the majority of its compounded drugs intrastate to be primarily overseen by the State, which is responsible both for regulation of the compounder and protection of its citizens who receive the compounded drugs. However, as discussed above, if a substantial proportion of a compounder’s drugs is distributed outside a State’s borders, adequate regulation of those drugs poses significant challenges to State regulators. In such cases, although State oversight continues to be critical, additional oversight by FDA may afford an important public health benefit.

As stated above, in the revised draft standard MOU, FDA proposes eliminating the 30 percent limit and instead establishing 50 percent as the threshold beyond which the amount of compounded drugs distributed interstate would be considered inordinate. Under this proposal, the threshold triggers an information collection and reporting obligation once it is reached. The Agency believes that more than 50 percent is an appropriate measure of “inordinate amounts”

because it marks the point at which pharmacies and physicians are distributing the majority of their compounded drug products interstate, and the regulatory challenges associated with interstate distributors discussed above become more pronounced. At this tipping point, the risk posed by the distribution practices of the compounder may weigh in favor of additional Federal oversight in addition to State oversight.

FDA recognizes that in some cases, compounders may distribute more than 50 percent of a small quantity of compounded drug products to contiguous States. Although such compounders have exceeded the inordinate amounts threshold proposed in the revised draft standard MOU, FDA would consider other information, such as the number of patients that will receive the compounded drugs, if available, when assessing the compounders' priority for risk-based inspection. Accordingly, when a State identifies a pharmacy or physician that distributes an inordinate amount of compounded drug products interstate, the draft standard MOU provides that the State would supply the Agency with: (1) information about the total number of prescription orders for compounded drug products that it distributed or dispensed intrastate; (2) the total number of prescription orders for compounded drug products that it distributed interstate; (3) the total number of prescription orders for sterile compounded drug products that it distributed interstate; (4) the number of States in which the compounder is licensed; and (5) whether the State inspected for and found during its most recent inspection that the compounding pharmacy or physician distributed compounded drug products without valid prescriptions for individually identified patients. FDA intends to use this information to prioritize its inspections of compounders based on risk, focusing on those that appear likely to distribute large volumes of compounded drug products, particularly when the distribution is to multiple States, the drug

products are intended to be sterile, and there is information about a lack of valid prescriptions for individually identified patients.

FDA has further revised the calculation of inordinate amounts as follows. The 2015 draft standard MOU provided that a compounder is considered to have distributed an inordinate amount of compounded drug products interstate if the number of units of compounded drug products distributed interstate during any calendar month is equal to or greater than 30 percent of the number of units of compounded and non-compounded drug products distributed or dispensed both intrastate and interstate by such compounder during that calendar month. FDA received comments noting that because the calculation includes both compounded and non-compounded drug products, in many cases, a substantial factor in whether a compounder has distributed an inordinate amount of compounded drug products interstate is whether the compounder offers non-compounded drug products. For example, under that policy, many specialty compounding pharmacies that engage in interstate distribution and only distribute compounded drug products would be able to distribute fewer compounded drug products interstate before reaching an inordinate amount than a pharmacy that also fills prescriptions for non-compounded drug products, even if both pharmacies produced the same amount of compounded drug products. After considering the public comments, FDA does not believe that including non-compounded drug products within the calculation of inordinate amounts would help address the public health concerns associated with sending compounded drug products out of State that Congress sought to address in section 503A(b)(3)(B) of the FD&C Act. Accordingly, for purposes of the revised draft standard MOU, FDA is proposing to exclude consideration of non-compounded drug

products from the calculation of inordinate amounts so that the denominator is determined by solely referencing compounded drug products.³

C. Definitions

Appendix A in the revised draft standard MOU defines key terms used in the MOU. FDA is retaining the definitions of “adverse drug experience,” “serious adverse drug experience,” “product quality issue,” and “serious product quality issue” from the 2015 draft standard MOU.

The revised draft standard MOU also defines “distribution.” With respect to that definition, for purposes of the revised draft standard MOU, FDA proposes that distribution means that a compounder has sent a compounded drug product out of the facility in which the drug was compounded. Such distribution may include, but is not limited to, delivery or shipment to a physician’s office, hospital, or other health care setting for administration, and dispensing the drug product by sending it to a patient for the patient’s own use. This definition is revised from the 2015 draft standard MOU and is intended to address stakeholder comments and to better effectuate the purposes of section 503A of the FD&C Act.

In the 2015 draft standard MOU, FDA proposed to define the term “distribution” to include, among other things, dispensing of a compounded drug product to a patient for the patient’s own use. We received a number of comments on the 2015 draft standard MOU stating that distributing and dispensing are mutually exclusive activities, such that if a drug product is distributed, it is not also dispensed, and vice versa. Some comments asserted, in particular, that a compounded drug product should not be considered to be “distributed” when it is provided pursuant to a prescription. Other stakeholders, however, agreed with the inclusion of drug

³ FDA also intends to exclude non-compounded drugs from the calculation of the 5 percent limit in section 503A(b)(3)(B)(ii).

products provided pursuant to a prescription within the definition of “distribution” and maintained that this interpretation was important to protect the public health.

After considering these comments and the public health objectives of section 503A(b)(3)(B) of the FD&C Act, we have proposed to revise the definition of distribution to exclude dispensing that occurs at the facility in which the drug was compounded. We intend to consider that when a drug is picked up in this way, dispensing, but not distribution, occurs for purposes of calculating “inordinate amounts” under the MOU or applying the 5 percent limit in section 503A(b)(3)(B)(ii) of the FD&C Act.

FDA proposes that in-person dispensing, where the transaction between the compounder and the patient is completed without the compounded drug leaving the facility in which it was compounded, is appropriately overseen, primarily, by the State outside the context of the MOU, regardless of whether the compounded drug product subsequently leaves the State. Such an intrastate, local transaction generally indicates a close connection among the patient, compounder, and prescriber. By contrast, transactions by mail often have a less direct nexus among the patient, compounder, and prescriber than in-person pickups and would be considered “distributions.”

Under this revised proposed definition, drugs dispensed in-person that are later taken out of State would not contribute to reaching the threshold for inordinate amounts that would need to be reported to FDA under the MOU. Nor would complaints associated with compounded drug products dispensed this way and subsequently taken out of State be subject to the complaint investigation provisions of the MOU. FDA expects that, in practice, the State in which the initial transaction occurred would handle such complaints. The State may, in its discretion, notify FDA of the complaint. We recognize that including in-person dispensing in the definition of

“distribution” would result in complex tracking issues in instances when a patient subsequently crosses State lines. Under the proposed revised definition, the compounder would not need to track where the patient takes the compounded drug product after it is in the patient’s possession.

FDA is not persuaded by comments on the 2015 draft standard MOU urging the Agency to interpret “distribution” and “dispensing” to be entirely separate activities for purposes of section 503A(b)(3)(B) of the FD&C Act. These comments recommend using definitions for these terms used elsewhere in the FD&C Act and FDA regulations, and generally conclude that distribution does not include the transfer of a drug pursuant to a prescription.

The conditions in section 503A, including section 503A(b)(3)(B), must be interpreted consistent with the prescription requirement in section 503A(a) of the FD&C Act. If we were to interpret the word “distribution” to apply only if a drug is provided without a prescription, it would mean that drug products compounded under section 503A of the FD&C Act are excluded from regulation under the MOU and the 5 percent limit, because to qualify for the exemptions under section 503A, a compounder must obtain a valid prescription order for an individually identified patient. For the reasons stated previously in section IV.B, we believe this would achieve the opposite of what Congress intended. A compounded drug product may be eligible for the exemptions under section 503A of the FD&C Act only if it is, among other things, “compounded for an identified individual patient based on the receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient.”

Nor is there anything to suggest that Congress understood distributed and dispensed to be mutually exclusive categories rather than overlapping categories for purposes of section 503A of the FD&C Act. Section 503A(b)(3)(B) of the FD&C Act does not define “distribution” to

exclude dispensing, which Congress has done elsewhere when that was its intention.⁴ The definition proposed by comments would write an exclusion for dispensing, in its entirety, into the statute where Congress did not. Indeed, with respect to comments suggesting that drugs dispensed pursuant to prescriptions could not also be “distributed,” we note that, in section 503A(b)(3)(B) of the FD&C Act, Congress specifically contemplated that prescription orders could be “distributed” when it directed the Agency to count the number of prescription orders that pharmacists and prescribers distributed.

V. Other Issues

A. Development of a Standard MOU

A number of comments on the 1999 draft standard MOU, the 2013 draft 503A guidance, and the 2015 draft standard MOU suggested that FDA negotiate MOUs with individual States, rather than develop a standard MOU. Section 503A of the FD&C Act requires the Agency to develop a standard MOU for use by the States. Furthermore, it would be impractical to develop an individualized MOU with every State, and creating individualized MOUs would create a patchwork of regulation of interstate distribution by compounders seeking to qualify for the exemptions under section 503A of the FD&C Act. This would be confusing to the health care community, as well as regulators.

⁴ In other (non-compounding) contexts, where it would further a regulatory purpose, Congress and the Agency have specifically defined “distribute” to exclude dispensing. See, for example, section 581(5) of the FD&C Act (21 U.S.C. 360eee(5)), which applies to Title II of the DQSA, and 21 CFR 208.3. Section 503A of the FD&C Act does not contain a similar definition or a similar specific direction to exclude dispensing from the meaning of distribution. We also note that these definitions were adopted for provisions that focus on conventionally manufactured drug products, which assign different obligations to dispensers than to wholesalers, packagers, or other intermediaries in light of the different role that dispensers play with respect to product labeling and the drug distribution chain. In contrast, section 503A of the FD&C Act focuses on compounded drugs, and the reasons for defining “distribution” to exclude dispensing in Title II of the DQSA or part 208 do not apply.

B. Exemptions From the Interstate Distribution Provisions

Some comments on the 2013 draft 503A guidance and the 2015 draft standard MOU requested that we consider exempting certain drug products or types of compounding entities from the threshold in the MOU and the 5 percent limit. For example, some comments recommended that we exempt nonsterile products.

American consumers rely on the FDA drug approval process to ensure that medications have been evaluated for safety and effectiveness before they are marketed in the United States. Drugs made by compounders, including those made at outsourcing facilities, are not FDA-approved. This means that they have not undergone premarket review of safety, effectiveness, or manufacturing quality. Therefore, when an FDA-approved drug is commercially available, FDA recommends that practitioners prescribe the FDA-approved drug rather than a compounded drug unless the prescribing practitioner has determined that a compounded product is necessary for the particular patient and would provide a significant difference for the patient as compared to the FDA-approved commercially available drug product.

In section 503A of the FD&C Act, Congress enacted several conditions to differentiate compounders from conventional manufacturers and provided that only if the compounders meet those conditions can they qualify for the exemptions from the drug approval requirements in section 505 of the FD&C Act. One of those conditions relates to limitations on the interstate distribution of compounded drug products, and FDA intends to enforce those provisions to differentiate compounding that qualifies for the exemptions from conventional manufacturing in the guise of compounding that does not, and will apply the conditions to all types of drugs and all categories of compounding.

C. Information Sharing Between States and FDA

The revised draft standard MOU provides that States will agree to notify FDA of any complaint relating to a compounded drug product distributed outside the State involving a serious adverse drug experience or serious product quality issue, and provide information about those events and issues. The revised draft standard MOU also provides that States will notify FDA if they identify a pharmacy or physician within their jurisdiction that has distributed inordinate amounts of compounded drug products interstate.

FDA regularly posts on its compounding website information about enforcement and other actions related to compounders that violate the FD&C Act, and it is obligated to share certain information with States under section 105 of the DQSA. In addition to these measures, FDA is taking steps to proactively share information with States about complaints that it receives, consistent with Federal laws governing information disclosure.

D. Enforcement of the 5 Percent Limit on Distribution of Compounded Drug Products Out of the State in Which They Are Compounded

In the 503A guidance, FDA stated that it does not intend to enforce the 5 percent limit on distribution of compounded drug products outside of the State in which they are compounded until 90 days after FDA has finalized a standard MOU and made it available to the States for their consideration and signature. Most comments on the 2013 draft 503A guidance said this period was too short, but did not recommend a specific alternative. A few comments recommended a different timeframe, one recommending 120 days and another recommending 365 days. The 1997 Senate Committee Report for the Food and Drug Administration Modernization Act suggests that a 180-day period for States to decide whether to sign might be

appropriate.⁵ Consistent with the 2015 draft standard MOU, the Agency proposes a 180-day period after the final standard MOU is made available for signature before FDA will enforce the 5 percent limit in States that have not signed the MOU, and invites public comment on whether this is an appropriate timeframe. FDA will announce at the time it publishes the final standard MOU and makes it available for signature when it intends to begin enforcing the 5 percent limit in States that do not sign.

E. Physician Compounding

Several comments advised that State boards of pharmacy do not oversee physician compounding and would not be able to agree to perform the obligations under the 2015 draft standard MOU with respect to oversight of physician compounding.

FDA recognizes that physicians often do not indicate, as part of their State licensure, that they compound drug products, and that there may not be routine mechanisms, such as inspections, to determine the extent to which such physicians distribute compounded drugs interstate. It is also FDA's understanding that physicians who compound drugs generally do so for their own patients, within their own professional practice, and they distribute or dispense them intrastate. However, there is still the potential for widespread harm if physicians ship large percentages of compounded drugs interstate without State investigation of complaints associated with those compounded drugs. Accordingly, under the revised draft standard MOU, States would agree to: (1) notify FDA and the appropriate State agency if they receive information about serious adverse drug experiences or serious product quality issues associated with drugs compounded by physicians and (2) if they become aware of a physician distributing compounded

⁵ “[U]ntil the State...enters into a memorandum of understanding (MOU) with the Secretary or 180 days after the development of the standard MOU, whichever comes first, the [section 503A] exemption shall not apply if inordinate quantities of compounded products are distributed outside of the State in which the compounding pharmacy or physician is located.” (U.S. Senate Committee Report)

drugs interstate, coordinate with the regulator of physician compounding within the State to determine whether the physician distributes inordinate amounts of compounded drug products interstate and notify FDA of physicians that do so.

F. Prescription Orders

Commenters expressed that the meaning of the term “units,” which is used in the 2015 draft standard MOU to calculate the 30 percent limit, was unclear to them.

In the revised draft standard MOU, FDA has replaced the term “unit” with “prescription order” (i.e., the inordinate amounts calculation uses numbers of prescription orders for compounded drug products). “Prescription orders” includes chart orders for patients made in a healthcare setting. For purposes of this MOU, each refill is considered to be a new prescription order.

VI. Paperwork Reduction Act of 1995

Under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501-3520), Federal Agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information they conduct or sponsor. “Collection of information” is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes Agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)), requires Federal Agencies to provide a 60-day notice in the *Federal Register* for each proposed collection of information before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing notice of the proposed collection of information set forth in this document.

With respect to the following collection of information, FDA invites comments on these topics: (1) whether the proposed collection of information is necessary for the proper

performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Section 503A of the FD&C Act describes, among other things, the circumstances under which certain drug products compounded by a licensed pharmacist or licensed physician are exempt from certain sections of the FD&C Act. One of the conditions to qualify for the exemptions listed in section 503A of the FD&C Act is that: (1) the drug product is compounded in a State that has entered into an MOU with FDA that addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such a State or (2) if the drug product is compounded in a State that has not entered into such an MOU, the licensed pharmacist, pharmacy, or physician does not distribute, or cause to be distributed, compounded drug products out of the State in which they are compounded, more than 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician (see section 503A(b)(3)(B)(i) and (ii)).

Section 503A(b)(3) directs FDA, in consultation with the NABP, to develop a standard MOU for use by States in complying with the provisions concerning the interstate distribution of inordinate amounts of compounded drug products interstate and appropriate investigation by a State agency of complaints relating to drug products compounded in the State and distributed outside such State.

The revised draft standard MOU contains the information collections that must be approved by OMB under the PRA. These information collections are described in this section of the document. For purposes of this analysis, FDA assumes that 45 States will sign the standard MOU with FDA.

Under section III.a. of the revised draft standard MOU, the State will notify FDA by email at StateMOU@fda.hhs.gov as soon as possible, but no later than 3 business days, after receiving any complaint relating to a compounded drug product distributed outside the State involving a serious adverse drug experience or serious product quality issue. The notification will include the following information: (1) the name and contact information of the complainant; (2) the name and address of the pharmacy or physician that is the subject of the complaint; (3) a description of the complaint, including a description of any compounded drug product that is the subject of the complaint; and (4) the State's initial assessment of the validity of the complaint relating to a compounded drug product distributed outside the State, if available. In addition, the States will maintain records of the complaints they receive, the investigation of each complaint, and any response to or action taken as a result of a complaint, beginning when the State receives notice of the complaint. The States will maintain these records for at least 3 years, beginning on the date of final action or the date of a decision that the complaint requires no action.

Based on our knowledge of State regulation of compounding practices and related complaints, we estimate that annually a total of approximately 45 States ("no. of respondents" in table 1, row 2) will notify FDA within 3 business days of receiving any complaint relating to a compounded drug product distributed outside the State involving a serious adverse drug experience or serious product quality issue. We estimate that each State will notify FDA annually of approximately 3 complaints it receives ("no. of responses per respondent" in table 1,

row 2), for a total of 135 notifications of complaints sent to FDA (“total annual responses” in table 1, row 2). We estimate that preparing and submitting this information to us as described in the MOU will take approximately 0.5 hours per response (“average burden per response” in table 1, row 1), for a total of 67.5 hours (“total hours” in table 1, row 2).

We also estimate that a total of approximately 45 States (“no. of recordkeepers” in table 2) will prepare and maintain records for 3 years of the complaints they receive, investigations of complaints, and any State action taken or response to complaints. We estimate that each State will receive approximately 3 complaints annually and will prepare and maintain approximately 5 records per each complaint the State receives, for a total of 15 records per State (“no. of records per recordkeeper” in table 2), and a total of 675 records annually across all States (“total annual records” in table 2). We further estimate that preparing and maintaining these records will take approximately 1 hour per record (“average burden per recordkeeping (in hours)” in table 2), for a total of 675 hours (“total hours” in table 2).

Under section III.b of the revised draft standard MOU, on an annual basis (at minimum), the State will identify, using surveys, reviews of records during inspections, or other mechanisms available to the State, compounding pharmacies that distribute inordinate amounts of compounded drug products interstate by collecting information regarding the total number of prescription orders for compounded drug products distributed or dispensed intrastate and the total number of prescription orders for compounded drug products distributed interstate. Similarly, the State will engage in the same efforts to collect this information if it becomes aware of a physician who is distributing compounded drug products interstate. If a pharmacy or physician has been identified as distributing inordinate amounts of compounded drug products interstate, the State will also collect information regarding: (1) the total number of prescription

orders for sterile compounded drug products distributed out of State; (2) the number of States in which the compounding pharmacy or physician is licensed or number of States into which the compounding pharmacy or physician distributes compounded drug products; and (3) whether the State inspected for and found during its most recent inspection that the compounding pharmacy or physician distributed compounded drug products without valid prescriptions for individually identified patients.

The States will notify FDA by email at StateMOU@fda.hhs.gov within 30 days of identifying a pharmacy/physician within their jurisdiction that has distributed inordinate amounts of compounded drug products interstate, as described in the revised draft standard MOU. The notification should include the name and address of the pharmacy/physician and the information that the States collected, described in the previous paragraph.

We estimate that annually a total of approximately 45 States (“no. of respondents” in table 1, row 3) will identify compounding pharmacies or physicians that distribute inordinate amounts of compounded drug products interstate. We estimate that each State will perform surveys or inspections of 150 pharmacies or physicians to identify this information (“no. of responses per respondent” in table 1, row 3). We estimate that this will take approximately 1 hour per response (“average burden per response” in table 1, row 3), for a total of 6,750 hours (“total hours” in table 1, row 3). We estimate that annually a total of 40 States (“no. of respondents” in table 1, row 4) will notify FDA of their finding that a pharmacy or physician has distributed inordinate amounts of compounded drug products interstate. We estimate that each State will notify FDA annually of approximately 50 findings it makes (“no. of responses per respondent” in table 1, row 4), for a total of 200 notifications (“total annual responses” in table 1, row 4). We estimate that preparing and submitting this information to FDA as described in the

MOU will take approximately 0.5 hours per response (“average burden per response” in table 1, row 4), for a total of 100 hours (“total hours” in table 1, row 4).

Under section V of the revised draft standard MOU, a State may designate a new liaison to the MOU by notifying FDA’s administrative liaison in writing. If a State’s liaison becomes unavailable to fulfill its functions under the MOU, the State will name a new liaison within 2 weeks and notify FDA.

We estimate that annually a total of approximately 13 States (“no. of respondents” in table 1, row 5) will notify FDA of a new liaison to the MOU. We estimate that each State will submit to FDA annually approximately 1 notification of a new liaison (“no. of responses per respondent” in table 1, row 5), for a total of 13 notifications of a new liaison (“total annual responses” in table 1, row 5). We estimate that preparing and submitting each notification as described in the MOU will take approximately 0.2 hours per response (“average burden per response” in table 1, row 5), for a total of 2.6 hours (“total hours” in table 1, row 5).

Under section VI of the revised draft standard MOU, a State may terminate its participation in the MOU by submitting to FDA a 30-day notice of termination.

We estimate that annually a total of approximately 1 State (“no. of respondents” in table 1, row 6) will notify FDA that it intends to terminate its participation in the MOU. We estimate that this State will submit to FDA annually approximately 1 notification of termination (“no. of responses per respondent” in table 1, row 6), for a total of 1 notification (“total annual responses” in table 1, row 6). We estimate that preparing and submitting the notification as described in the MOU will take approximately 0.2 hours per notification (“average burden per response” in table 1, row 6), for a total of 0.2 hours (“total hours” in table 1, row 6).

Under section VI of the revised draft standard MOU, if a State does not adhere to the provisions of the MOU, FDA may post a 30-day notice of termination on its website. As a result of this action by FDA, the State will notify all licensed pharmacists, pharmacies and physicians within the State of the termination and advise them that compounded drug products may be distributed (or caused to be distributed) out of the State only in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician.

We estimate that annually a total of approximately 1 State (“no. of respondents” in table 3) will submit to the pharmacists, pharmacies, and physicians in its State 1 notification of termination as described in the MOU (“no. of disclosures per respondent” in table 3), for a total of 1 notification of termination (“total annual disclosures” in table 3). We estimate that preparing and submitting each notification will take approximately 1 hour per notification (“average burden per disclosure (in hours)” in table 3), for a total of 1 hour (“total hours” in table 3).

FDA estimates the burden of this collection of information as follows:

Table 1.--Estimated Annual Reporting Burden¹

Compounding MOU Between FDA and States	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
State notifies FDA of compounding complaints it receives	45	3	135	0.5 (30 minutes)	67.5
State identifies pharmacies or physicians that distribute inordinate amounts of compounded drugs interstate using surveys or inspections	45	150	6,750	1	6,750
State notifies FDA of the distribution of inordinate amounts of compounded drug products	40	50	200	0.5 (30 minutes)	100
State notifies FDA of a new liaison to the MOU	13	1	13	0.2 (12 minutes)	2.6
State notifies FDA of its intent to terminate participation in the MOU	1	1	1	0.2 (12 minutes)	0.2
Total					6,920.3

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 2.--Estimated Annual Recordkeeping Burden¹

Compounding MOU Between FDA and States	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping (in Hours)	Total Hours
State recordkeeping for 3 years of compounding complaints	45	15	675	1	675
Total					675

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 3.--Estimated Annual Third-Party Disclosure Burden¹

Compounding MOU Between FDA and States	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure (in Hours)	Total Hours
State notification to pharmacists, pharmacies, and physicians that its participation in the MOU has been terminated by FDA	1	1	1	1	1
Total					1

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

III. Electronic Access

Persons with access to the internet may obtain the draft MOU at either

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

or <https://www.regulations.gov>.

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Leslie Kux,

Associate Commissioner for Policy.

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